REMARKS

In the Final Action dated August 25, 2004, claims 18-20 are pending and are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Green et al. (The Veterinary Record, May 2, 1987) and Geresi et al. (Ann. Immuno. Hung 25:37-40, 1985) in view of Wu et al. (J. Immunol. 148:1519-1525, 1992) and Gluck et al. (U.S. Patent No. 5,879,685).

Claims 18-20 are directed to a multicomponent clostridial vaccine composition comprising at least two species or serotypes of Clostridium, a retroviral antigen and a saponin adjuvant. Applicants previously submitted that there is no suggestion anywhere to combine the teachings of the cited references to produce the claimed vaccine composition. In addition, Applicants argued that the results achieved with the presently claimed vaccine composition are unexpected.

In response, the Examiner acknowledges that obviousness can only be established by combining or modifying the teachings of the prior art where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The Examiner argues that in this case, the motivation of combining immunogenic compositions containing a *Clostridium* species and a respiratory virus is coming from teachings of Gluck et al. Gluck et al. teach an immunostimulating combination of an influenza virus and *Clostridium tetani*. Further, the Examiner argues that use of different adjuvants, such as saponin, in a vaccine preparation is well known in the art, and that a saponin adjuvant is commercially available (i.e. Quil A) (see Wu et al. page 1519, right column). Therefore, the Examiner concludes that one of ordinary skill

in the art would have been motivated to replace the aluminum hydroxide adjuvant of Green et al. with a saponin adjuvant.

Applicants respectfully disagree with the Examiner. Applicants acknowledge that Gluck et al. teach a combination of a *Clostridium* species with a respiratory virus. Applicants also acknowledge that saponins were commercially available and may have been used as an adjuvant in association with antigens that are not *Clostridium*. However, Applicants respectfully submit that there is no suggestion in the art to employ a saponin adjuvant in combination with a *Clostridium* antigen. The fact that saponin was commercially available and was successfully used in combination with non-*Clostridium* antigens would not necessarily suggest to, or motivate, those skilled in the art to combine a saponin adjuvant with a *Clostridium* antigen, especially in light of the relatively low antigenicity and poor stability of *Clostridium* antigens known in the art, and in view of the teaching of Wu et al. away from the claimed invention.

More specifically, prior to the present invention, it was generally recognized that clostridial toxoids were soluble proteins of relatively low antigenicity and poor stability; and thus, clostridial vaccines required adjuvants, typically, aluminum compounds, in order to increase antigenic potency and to enhance stability. Aluminum compounds were capable of adsorbing and/or precipitating clostridial toxoids, as well as retaining the toxoids at the injection site. However, as described in the specification at page 1, lines 35-37, aluminum compound-based adjuvants often provoked severe persistent local reactions, such as granulomas, abscesses and scarring, when injected subcutaneously or intramuscularly. The present inventors have uniquely recognized that stable, potent, multicomponent clostridial vaccines can be made with a rapidly dispersed, soluble adjuvant, such as a saponin, without the use of a depot adjuvant such as an aluminum compound.

Furthermore, rather than providing a suggestion or motivation to those skilled in the art to obtain the claimed vaccine, as the Examiner has alleged, Wu et al. clearly teach away from the presently claimed invention. Applicants respectfully direct the Examiner's attention to the cited reference, Wu et al., which clearly showed that a saponin adjuvant, when used alone without alum, did not have any adjuvant effect. Specifically, in Figure 2 at page 1521, Wu et al. demonstrated that the immunostimulating effect of the saponin adjuvant, QS-21, was observed only when the saponin was used in combination with alum, not when used alone. Therefore, Applicants respectfully submit that Wu et al. would not have provided any motivation to those skilled in the art to make a vaccine composition with a saponin adjuvant without an aluminium compound.

It is noted that the Examiner has not responded to Applicants' argument that Wu et al. teach away from the claimed invention. Rather, the Examiner refers to page 1524 of Wu et al., where Wu et al., in referring to two publications by Frebbe et al., comment that a saponin mixture has been shown to augment antibody responses. As submitted above, Applicants do not dispute that saponin adjuvants may have been successfully used in combination with non-*Clostridium* antigens. However, the art, particularly the explicit showing by Wu et al., clearly recognizes that the immuno-potentiation effect of saponin may depend on the concomitant use of an alum-based adjuvant. See Figure 2 of Wu et al. (compare QS21 plus alum with QS21 alone or alum alone).

Applicants further respectfully submit that none of the remaining references provide any suggestion or motivation to those skilled in the art to combine the respective teachings of each other. In this regard, Green et al. teach a vaccine composition employing an aluminum hydroxide adjuvant, which is specifically described in the present application as unsuitable for

use in the claimed clostridial vaccine composition. Thus, Green et al. also teach away from the composition of the present invention. Geresi et al. fail to teach the use of any adjuvant, let alone a soluble adjuvant such as a saponin. Gluck et al. do not teach or even suggest the use of saponin as an adjuvant in the vaccine disclosed therein.

Accordingly, Applicants respectfully submit that none of the cited references, taken alone or in combination, provide any teaching or suggestion that would have motivated those skilled in the art to combine the respective teachings of the references in order to arrive at the presently claimed vaccine composition.

In response to Applicants' arguments with respect to unexpected results, the Examiner states that use of soluble adjuvants that are readily dispersed from the injection site and has no depot effect, such as saponin, is routine in the art of vaccine preparation. Again referring to page 1524 of Wu et al., the Examiner indicates that Quil A, a saponin mixture, has been shown to augment antibody responses.

In the first instance, Applicants respectfully submit that given the known low antigenicity and poor stability of clostridial antigens, and the recognition in the art (as shown in Wu et al.) that the immuno-potentiating property of saponin may depend on the concomitant use of an alum-based adjuvant, it is certainly unexpected for the present inventors to show that saponin, alone and absent an alum-based adjuvant, would be successful in enhancing the potency of clostridial antigens.

Furthermore, Applicants respectfully submit that the claimed vaccine manifests unexpected results and superior properties in that a saponin-adjuvanted vaccine containing seven clostridial antigens is safer and more effective than a vaccine containing the same clostridial antigens and aluminium hydroxide gel as adjuvant. In this connection, Applicants direct the

Examiner's attention to the specification, at pages 13-18, where multicomponent clostridial vaccines containing a saponin adjuvant were compared to vaccines containing the same clostridial components but with aluminium hybroxide gel as adjuvant. As described at pages 14-15, while the $Al(OH)_3$ gel-adjuvanted vaccines provoked chronic local reactions (such as swelling) for an extended period (e.g., 6 weeks), the saponin-adjuvanted vaccine only induced transient reactions at the injection sites that disappeared quickly after a few days. In addition, the saponin-adjuvanted vaccine containing seven clostridial antigens induced stronger antibody response against *C. chauvoei* than a vaccine containing the same clostridial antigens and aluminium hydroxide gel as adjuvant.

In view of the foregoing, it is respectfully submitted that the cited references, alone or in combination, do not render the claimed vaccine obvious. As such, the rejection of claims 18-20 under 35 U.S.C. §103(a) over Green et al. and Geresi et al. in view of Wu et al. and Gluck et al., is overcome. Withdrawal of the rejection is therefore respectfully requested.

Accordingly, it is respectfully submitted that the application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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